Chapter 2

Microbiological findings and adequacy of antibiotic treatment in the critically ill patient with drowning-associated pneumonia

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Abstract

Introduction

To identify risk factors for the development of drowning-associated pneumonia and for non-survival during ICU admission. Secondly, we aim to describe micro-organisms causing drowning-associated pneumonia and to compare these to micro-organisms cultured from locally retrieved water samples.

Methods

All adult drowning victims admitted to the ICU between 2001 and 2012 were included. Clinical and microbiological findings within the first week of admission were compared between patients with and without a drowning-associated pneumonia and early risk factors were analysed for non-survival. Water samples were retrieved from different common drowning sites in the area, and compared with microbiological findings attained from patients with pneumonia.

Results

Forty-nine patients were included of which 18 patients developed a pneumonia in the first week of admission. Patients with pneumonia showed a higher body-mass-index than the patients without. Nineteen patients died during their ICU stay. Out of hospital cardiac arrest before ICU admission, the need for mechanical ventilation, pH of lower than 7.10 on admission, a high lactate level and age of over 50 years were risk factors for non-survival. *Aeromonas* spp. and *Staphylococcus aureus* were the predominantly cultured micro-organisms in patients developing drowning-associated pneumonia and from the water samples. Three different species of *Aspergillus* were cultured from the different water sites.

Conclusion

Early risk factors for non-survival are circulatory arrest before ICU admission, the need for mechanical ventilation, a baseline pH of lower than 7.10 or higher lactate and age of over 50 years. Antibiotic and antifungal treatment against gram-negative waterborne bacteria and *Aspergillus* spp seems a rational choice in patients with a drowning-associated pneumonia.

Introduction

According to the latest definitions, drowning is defined as the process of primary respiratory impairment from submersion or immersion in a liquid medium. The victim may live or die after this process, but despite the outcome, he or she has been involved in a drowning incident.[1] Worldwide drowning accounts for approximately 500.000 deaths per year.[2] The most common cause of death caused by drowning is hypoxemia and resultant cerebral hypoxia induced by pulmonary injury.[3]

Infection and thereby pneumonia is another potential life-threatening complication in drowning victims.[4] One of the main factors contributing to the risk of developing pneumonia after drowning is aspiration of water or gastric contents. It has been estimated that approximately 90% of patients aspirate water during drowning and 10% die of dry asphyxia caused by laryngospasm. Additionally it has been demonstrated that approximately 70% of drowning victims aspirate foreign material such as mud, algae and vomitus, which contributes to the risk of developing pneumonia.[3-6] Other factors, such as water temperature and composition of the water (fresh or salt) seem to have a less clear role. Alongside the risk of developing drowning-associated pneumonia, drowning victims are also at risk of developing nosocomial pneumonia, due to damage of the epithelial lining of the airways and mechanical ventilation.[4-7]

Diagnosing pneumonia in drowning victims is difficult since many drowning victims develop chest radiological abnormalities and not seldom fever occurs without a clear focus for infection.[8,9] Cultures taken from these patients are often difficult to interpret as they may represent true pathogens, airway colonization or contamination from the environment.[4]

The use of prophylactic antibiotics is controversial, because they contribute to selection of more resistant and aggressive micro-organisms.[3,4,7,10,11] On the other side, if patients present with early signs of infection or have risk factors like drowning in heavily contaminated water or warm water temperature broad-spectrum prophylactic antibiotics can be considered. [3,12] Bacteria causing pneumonia in drowning victims are often waterborne or from oropharyngeal origin. Fungi have also been described in the literature as a cause of pneumonia in drowning victims.[4,7,13-16] However, administration of empirical antifungals is questionable.

The main aim of this study was to identify risk factors for the development of drowning-associated pneumonia and for non-survival during ICU admission. Secondly, we aim to describe micro-organisms causing drowning-associated pneumonia and to compare these to micro-organisms cultured from locally retrieved water samples.

Methods

According to Dutch legislation, no approval of the research ethics committee was required for this retrospective study as long as data were anonymized. This is a retrospective study of all patients admitted to the Intensive Care Unit of the VU University medical center Amsterdam after a drowning accident from February 2001 until June 2012. Patients were traced using computerized queries of the patient data management system (MetaVision®, Tel Aviv, Israel). Patient records were reviewed for demographics, APACHE II score, drowning data, clinical and microbiological findings, diagnostic tests, treatment and outcome. In addition, the lung injury score (LIS), the sepsis-related organ failure assessment (SOFA) and the clinical pulmonary infection score (CPIS) were calculated on day 0, 1, 2, 4 and 6 from admission.[17-20] Additionally, micro-organisms responsible for the development of drowning-associated pneumonia were described and risk analysis for mortality was performed. Furthermore, samples of water retrieved from the canals of Amsterdam, a local lake and a wide ditch near Amsterdam were retrieved and cultured micro-organisms were compared to those found in cultures of patients with pneumonia.

Definitions

In this study patients were diagnosed with drowning-associated pneumonia, when having new or persistent chest radiographic evidence for pneumonia, a potentially pathogenic micro-organism cultured from a tracheal aspirate or broncho-alveolar lavage fluid and two of the three following criteria: fever (temperature $\geq$ 38,0°C), purulent endotracheal secretions, leucocytosis (leucocytes > 10,0 x 10^9 / L) or leucopenia (leucocytes < 4,0 x 10^9 / L). These criteria and radiographic evidence for pneumonia needed to be present within a range of 24 hours of positive culture to diagnose drowning-associated pneumonia. Only cases of pneumonia diagnosed within the first week of admission were taken into account.

Water samples

The drowning site was extracted from the medical reports and ambulance data. Many drowning incidents took place in ‘het Nieuwe Meer’, ‘de Sloterplas’ and the canals of Amsterdam as these lie within close proximity to the VU medical center Amsterdam. We collected and cultured water samples from these sites and compared micro-organisms cultured from the water to those cultured from tracheal aspirate or broncho-alveolar lavage fluid of patients who developed drowning-associated pneumonia. From each water sample we collected, six times one hundred milliliters of water was filtered through a nitrocellulose membrane (Sartorius cellulose nitrate filter, 0.45 µm) and the membranes were cultured on six different agars. The agars consisted of 2 Sabauroud sodium agars (manufactured in-house, aerobically incubated at 25 ºC and 37ºC for 2 weeks), a sheep blood agar and a Mac-Conkey agar (Biomérieux, both aerobically incubated for 24 hours) and 2 selective media, a Karmali agar (Oxoid, micro-aerophilically incubated for 72 hours) for *Campylobacter* spp and a TCBS agar (Mediaproducts BV, aerobically incubated for 24 hours) for *Vibrio* spp. All gram-negative bacteria were determined by the Vitek 2 system and some were also tested with the Vitek MS system (Biomérieux). All relevant gram-positive rods and cocci were determined using Gram staining, biochemical tests or API 20 STREP (Biomérieux). A *Vibrio cholera* agglutination test was performed if necessary. Relevant moulds were determined by microscopy and in case of *Aspergillus* spp., resistance was determined using E-tests (Biomérieux) on RPMI agars (manufactured in-house, incubated for 48 hours). Interpretation of inhibition zones was made according to current Clinical and Laboratory Standards Institute (CLSI) guidelines.

Statistical analysis

Statistical analysis was performed using SPSS version 20. Patients were classified into two groups: patients who developed drowning-associated pneumonia within the first week of admission (pneumonia patients) and patients without drowning-associated pneumonia (non-pneumonia patients). Data were expressed as median (range) or as number of patients where appropriate. Fisher Exact's or Mann-Whitney U tests were used where appropriate. After univariate analysis backward multivariate logistic regression was performed, to analyse risk factors for non-survival. However, due to the small study population it was performed with three most significant variables. Tests were two-sided and a P-value <0.05 was considered statistically significant. For non-survival a correction for multiple testing was performed by a P-value of 0.01.

Results

Baseline characteristics

From February 2001 until June 2012, 49 drowning victims were admitted to the Intensive Care Unit with a median age of 38 years of which 86% was male (Table 1). Of the 49 drowning victims, 18 (37%) developed pneumonia in the first week of admission. Patients who developed pneumonia showed a higher BMI (26.7 ± 4.4 versus 24.0 ± 2.6; $P = 0.016$). Three patients died within 24 hours of admission and were excluded from further analysis. Most patients drowned in the canals of Amsterdam or in local lakes. Patients who developed pneumonia had a significant prolonged length of stay in the ICU and in hospital. No significant difference in mortality rate was found between patients who did or did not develop pneumonia.

Table 1 Drowning victims with and without pneumonia			
	Pneumonia patients	**Non-pneumonia patients**	***P*-value**
Patients	18 (37%)	31 (63%)	
Age (years)	43 [30-70]	35 [24-53]	**0.40**
Gender (male)	16 (89%)	26 (84%)	**1.00**
BMI	26.7 ±4.4	24.0 ±2.6	**0.016**
Drowning			
Estimated duration (minutes)	7.6 (5,3)	12.6 (8,4)	**0.057**
Fresh water (opposed to sea water)	16 (100%)	22 (96%)	**1.00**
Canal water	5 (56%)	3 (30%)	**0.37**
Findings on admission			
Body temperature (°C)	32.7 [30.4-34.2]	32.0 [30.7-34.7]	**0.69**
Out-of-hospital cardiac arrest before admission	11 (68.8%)	19 (67.9%)	**0.95**
First measured pH	6.89 ±0,29	6.95 ±0.34	**0.54**
Sodium (mmol/ml)	137 ±5	139 ±5	**0.19**
Leucocyt count (x 10^9 / L)	12.2 [7.7-16.7]	8.6 [3.7-13.9]	**0.22**
Treatment			
Mechanical ventilation needed	17 (94%)	24 (80%)	**0.23**
Inotropic therapy needed on admission	16 (89%)	21 (68%)	**0.17**
Prophylactic antibiotics and/ or antifungals	18 (100%)	27 (87%)	**0.28**
Corticosteroids during admission	11 (69%)	15 (60%)	**0.57**
Survival	11 (61%)	19 (61%)	**0.99**
Length of stay on ICU (days)	10.5 [4.0-19,5]	3.0 [2.0-14.0]	**0.004**
Length of stay in hospital (days)	17.5 [6,3-27,0]	6.0 [2.0-17.0]	**0.019**

Data are expressed as mean ±SD, median [interquartile range] BMI (Body Mass Index)

<u>Survival</u>

Forty-nine patients were analysed and divided in survivors and non-survivors: 19 patients died (39%) during ICU stay (Table 2). Within the non-survivors significantly more patients were older than 50 years compared to survivors (11 [58%) versus 8 [27%] patients, retrospectively; *P*=0.03). Ninety percent of the non-survivors showed an out of hospital cardiac arrest before ICU admission versus 52% of survivors ($P<0.01$). Within the non-survivors group 89% of the patients showed a pH below 7.10 compared to 55% of the survivors ($P=0.01$). Non-survivors had higher lactate levels ($P<0.001$), a lower body temperature ($P<0.05$) and a higher APACHE II-score ($P<0.001$) compared to survivors. Within non-survivors all patients were in need of mechanical ventilation in comparison to 76% in the survivors ($P=0.03$). Backward stepwise logistic regression analysis showed age higher than 50 years as risk factor for non-survival ($P=0.01$).

<u>Micro-organisms</u>

Aeromonas spp. and *Staphylococcus aureus* were the predominantly found micro-organisms in patients developing pneumonia (Table 3). Positive sputum and broncho-alveolar lavage fluid cultures were retrieved within 48 hours of admission in 16 of the 18 patients with pneumonia. One patient developed *Aspergillus fumigatus* pneumonia, with a positive culture on day 5 of admission, after already being diagnosed with drowning-associated pneumonia caused by *Aeromonas spp*. This patient was initially treated with piperacillin plus tobramycin later on followed by voriconazole.

One patient developed drowning-associated pneumonia with a positive sputum culture yielding only *Flavobacterium odoratum*. This patient had radiological evidence for pneumonia and had high fever, leucocytosis and purulent sputum. Empirical antibiotic treatment consisted of piperacillin plus tobramycin. The patient was admitted after out-of-hospital cardiac arrest and imaging showed ischemia of the basal ganglia. After a month the patient was discharged from the ICU in a vegetative state. Once discharged from the ICU the patient kept having periods of high fever and developed pulmonary embolisms. After 99 days of admission in the hospital the patient died from pulmonary embolisms.

<u>Antimicrobial treatment</u>

Patients were given antimicrobials and all patients in need for mechanical ventilation received SDD (selective bowel decontamination) according to our local guidelines. In almost all patients antibiotic therapy was given directly on admission. The predominantly used initial antibiotic regimen was piperacillin plus tobramycin (25 patients; 51%), followed by ceftazidim plus tobramycin (5 patients; 10%). Antifungal therapy was administered in 20 patients (41%). The most commonly used antifungal agent was voriconazole (9 patients; 18%). Antimicrobial therapy was adequately covering cultured micro-organisms in 16 of the 18 pneumonia patients (89%). Two patients did not receive adequate therapy. From one *Aspergillus fumigatus* was cultured and the other received cefotaxim and a single gift of amoxicillin/clavulanic acid while culture revealed *Staphylococcus aureus* and *Serratia marcesens*.

Table 2 Univariate risk analysis for non-survival

	Non-survival	Survival	*P*-value
Patients	19 (39%)	30 (61%)	
Age > 50 years	11 (58%)	8 (27%)	**0.03**
Gender (male)	17 (90%)	25 (83%)	0.69
BMI	24.5 [21.5-29.2]	24.7 [23.2-26.8]	0.75
Drowning			
Estimated duration (minutes)	12.3 ±7,6	8.8 ±7,5	0.20
Fresh water (opposed to sea water)	15 (94%)	23 (100%)	0.41
Canal water	3 (50%)	5 (39%)	1.00
Findings on admission			
Bodytemperature (°C)	31.8 [29.8-32.9]	33.3 [31.0-35.6]	**0.03**
Out-of-hospital cardiac arrest before admission	17 (90%)	13 (52,0%)	**0.008**
pH < 7.10	17 (89%)	16 (55%)	**0.012**
Lactate (mmol/ml)	17.5 [9.9-27.8]	9.0 [3,0-15,3]	**0.001**
Glasgow Coma Scale by ambulance personnel	3 [3-3]	3 [3-7]	0.13
Glasgow Coma Scale on admission	3 [3-3]	3 [3-15]	**0.042**
Treatment			
Mild Hypothermic Treatment	15 (88%)	10 (83%)	1.00
Mechanical ventilation	19 (100%)	22 (76%)	**0.033**
Inotropic therapy on admission	16 (84%)	21 (70%)	0.32
Antibiotics	18 (95%)	27 (90%)	1.00
Pneumonia			
Pneumonia in the first week of admission	7 (37%)	11 (37%)	0.99
Scores			
APACHE II	36.0 ±5.1	25.7 ±11,1	**0.0003**
Cumulative SOFA score	51.7 ±10.0	46.5 ±11.3	0.47
CPIS score on admission	6.56±1.6	6.35±2.5	0.76
Lung Injury Score on admission	2.9±0.8	2.7±1.2	0.48

Data are expressed as mean ±SD, median [interquartile range] or number (percentages).
Percentages are from number of patients of which data was present.
To correct for multiple testing a P-value of 0.01 was set.
BMI = body mass index, ICU = intensive care unit.

Table 3 Cultured micro-organisms from sputum or broncho-alveolar lavage fluid in drowning victims	
Micro-organism	**n**
***Aeromonas* spp.**	9
Staphylococcus aureus	7
***Pseudomonas* spp.**	3
Haemophilus influenzae	3
Streptococcus pneumoniae	2
***Klebsiella* spp.**	2
Enterobacter cloacae	2
***Acinetobacter* spp.**	2
Stenotrophomonas maltophilia	2
Streptococcus pyogenes	1
Citrobacter freundii	1
Escherichia coli	1
Undetermined gram negative rod	1
Bacillus cereus	1
Serratia marcescens	1
Flavobacterium odoratum	1
Aspergillus fumigatus	1

Data are expressed as the total number of positive cultures in patients

Water samples

A water sample was retrieved from three different nearby drowning sites. These sites were chosen because most patients in this study drowned in these waters and are representative for water areas around the VU University medical center. Cultures of these water samples yielded many different micro-organisms (Table 4). Many of the micro-organisms cultured from the water samples were also derived from sputum- or broncho-alveolar lavage cultures in pneumonia patients. All three water samples showed *Aeromonas* spp. and three different species of *Aspergillus* were cultured. No resistance for azoles was found among the *Aspergillus* spp.

Table 4 Micro-organisms cultured from water samples			
	Canals	**'Het Nieuwe Meer'**	**'Sloterplas'**
Aeromonas sobria	X	X	X
Aeromonas salmonicida		X	X
Aeromonas hydrophila/caviae		X	
Pseudomonas aeruginosa			X
Escherichia coli	X		X
***Klebsiella pneumoniae* ssp**	X	X	
Shewanella putrefaciens	X		
Proteus mirabilis	X		
***Enterobacter cloacae* ssp**	X		
***Vibrio cholerae* (non-O1 type)**		X	
Bacillus cereus	X	X	X
Enterococcus faecium			X
Staphylococcus aureus			X
***Penicillium* spp.**		X	
***Paecilomyces* spp.**		X	
Zygomycetes	X		
Aspergillus niger	X		
Aspergillus fumigatus	X		
Aspergillus nidulans			X

X = micro-organism cultured from retrieved water sample

Discussion

The aim of this study was to search for associated clinical variables within the development of drowning-associated pneumonia. Additionally, we aim to identify risk factors for non-survival in drowning-associated pneumonia and to compare and describe cultured micro-organisms from our patients with the retrieved water samples. In univariate analysis it was shown that high BMI was associated with the development of pneumonia in the first week after drowning.

Our findings concerning the relation between high BMI and pneumonia are in line with other studies concerning overweight and obesity and the increased susceptibility to develop pneumonia.[21,22] A possible explanation might be that overweight and obese patients may have increased susceptibility to lower respiratory tract infection due to impaired T- and B-cell-mediated immune responses. Furthermore, they have a reduced lung volume and an altered ventilation pattern. Obesity is also related to other major chronic diseases that may increase the risk of pneumonia, including diabetes, heart failure, stroke, asthma and gastro-oesophageal reflux pattern. [22-24] Another possible explanation might be that the dose of the antibiotic treatment or prophylaxis was not sufficient in overweight and obese patients.

The incidence of pneumonia in the first week after drowning was almost 40%. This is in line with the incidence of pneumonia found by Oakes et al. and by Klein et al. although the definitions of pneumonia are not clearly stated in these studies.[11,25] Other studies report on a lower incidence of pneumonia after drowning.[7,26] A possible explanation for the relatively high incidence in our cohort, may be the fact that a lot of patients in our study drowned in the canals of Amsterdam. These are known to be heavily polluted with many different pathogens, as also confirmed by our findings.[27] Furthermore, as van Berkel et al. also stated about the Leiden area, many local lakes around the VU Medical Center Amsterdam harbour a variety of aquatic birds who add to the pollution of the water with their excreta.[7] This may also have contributed to the observed high incidence of pneumonia found in our population. We want to emphasize the fact that the incidence of pneumonia was relatively high even while most patients in our population received early adequate empirical antibiotics.

Our cohort of adult drowning victims is characterized by a high mortality rate reflecting high severity of the drowning incident. Most prominent early risk factors for non-survival in our cohort were out of hospital cardiac arrest, a base-line pH of lower than 7.10, a high lactate on arrival in the ER, the need for mechanical ventilation, and an age of over 50 years, which was in line with previous publications.[11,12] A lower body temperature did not seem to have a protective role in case of survival, like with induced hypothermia whereby a core temperature is maintained between 32°C and 34°C for 24 hours. However, with submersion hypothermia probably reflects a prolonged submersion time and thereby a higher mortality rate.[12]

Our microbiological findings imply that antibiotic coverage of *Staphylococcus aureus* and gram-negative waterborne bacteria like *Aeromonas spp.* is mandatory. *Staphylococcus aureus* and some of the other cultured micro-organisms that were found in our patients are known to colonize the upper oropharyngeal tract. These bacteria might have caused pneumonia by aspiration of contaminated water, but also by migration from the oropharyngeal tract into the lungs during aspiration. Another possible explanation may be that we are dealing with colonization of the oropharyngeal tract and not the real cause of pneumonia.

Study limitations:

We included only 49 patients, however only few other studies report on more patients. Some data were unavailable due to the retrospective design of our study. Furthermore, almost all of our patients received antibiotics.

Concerning the water samples it should be stressed out that we did not expect a direct answer to the question whether the micro-organisms in the water were the same as found in our patients. Obviously many patients drowned years ago and the microbiological composition of water is known to change over the years. Furthermore micro-organisms found in water vary over different seasons and vary with different temperatures. The water samples we retrieved were all taken from the waterfront and from one meter deep at the most, while many drowning victims might have drowned in deeper water and further away from the waterfront. Despite these limitations, we found a remarkable relation between the micro-organisms cultured from sputum- or broncho-alveolar lavage fluid in pneumonia patients and micro-organism cultured from the water samples. The most common pathogenic micro-organisms found in pneumonia patients were also cultured from the water samples and those not cultured might very well have been bacteria already colonizing the oropharyngeal tract. Comparing cultured micro-organisms in patients with drowning-associated pneumonia to micro-organisms cultured from drowning sites has been done before by others using water samples collected from respectively the river Seine, France and a river near San Antonio, Texas.[5,29] Our findings suggesting a relationship between the micro-organisms cultured from water samples and the micro-organisms cultured from patients with drowning-associated pneumonia, are in line with these studies. *Vibrio cholerae* was one of the more remarkable cultured micro-organisms from the water samples. Although it was not the endemic toxine producing serotype O1 that causes severe diarrhea, this non-O1 serotype can also cause infections, even sepsis in immunocompromised patients. This finding confirms that the waters around Amsterdam can be polluted with many different pathogens.

In conclusion, we found that from clinical parameters only a higher BMI was significantly associated with the development of pneumonia in the first week after drowning. Out of hospital cardiac arrest before ICU admission, the need for mechanical ventilation, pH of lower than 7.10 on admission, high lactate and age of over 50 years were risk factors for non-survival.

In this study *Aeromonas spp.* and *Staphylococcus aureus* were the most commonly cultured micro-organisms within patients admitted with drowning-associated pneumonia as well as directly from the water samples in the Amsterdam region. These cultures from nearby water areas confirmed the correct choice of antibiotic and when decided to start antibiotic treatment it should at least be directed against these micro-organisms and antifungal treatment should cover *Aspergillus* spp.

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